

# Relationship Between Serum Homocysteine and Other Parameters in Renal Transplant Patients

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• Available online 16 September 2009.

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## Abstract

### Introduction

Hyperhomocysteinemia frequently occurs after renal transplantation. We therefore assessed whether serum homocysteine (Hcy) concentrations were correlated with clinical, paraclinical, and arterial Doppler parameters among renal transplant patients.

### Methods

A cross-sectional study was performed on 47 patients (30 males, 17 females) who received unrelated living donor renal transplants.

### Results

The mean serum Hcy concentration was  $21.7 \pm 8.4$   $\mu\text{mol/L}$  (range = 5.8–48  $\mu\text{mol/L}$ ); 37 patients (79%) showed hyperhomocysteinemia (Hcy  $\geq 15$   $\mu\text{mol/L}$ ).

Serum Hcy was strongly related to body mass index (BMI;  $r = .43$ ,  $P = .002$ ), cyclosporine trough level ( $r = .44$ ,  $P = .005$ ), and serum creatinine concentration ( $r = .32$ ,  $P = .028$ ), but not to age, transplant duration, or sex. Multivariate analysis showed that only BMI ( $P = .003$ ) and cyclosporine trough level ( $P = .0037$ ) were independent predictors of serum Hcy concentrations. Hyperhomocysteinemia was more prevalent among patients taking mycophenolate mofetil (MMF) than azathioprine (86% vs 50%;  $P = 0.017$ ). The hyperhomocysteinemia and normohomocysteinemia groups did not differ significantly in mean carotid intima-media thickness (IMT;  $0.78 \pm 0.348$  vs  $0.77 \pm 0.419$  mm,  $P = .97$ ) or mean intrarenal resistive index (RI) ( $0.7 \pm 0.06$  vs  $0.7 \pm 0.06$ ,  $P = .85$ ). The two groups also did not differ in sex prevalence, diabetes, C-reactive protein  $\geq 5$  mg/L, or mean low-density lipoprotein, high-density lipoprotein, and mean arterial pressure (MAP) values.

## Conclusion

Serum Hcy correlated with higher cyclosporine trough levels and obesity. Hyperhomocysteinemia was more common among patients taking MMF than azathioprine, but had no effect on intrarenal RI or carotid IMT.

An increased prevalence of hyperhomocysteinemia has been observed in renal transplant recipients. [1] [2] [3] and [4] Intermediate and moderate hyperhomocysteinemia has been defined as plasma homocysteine (Hcy) concentrations of 31 to 100  $\mu$  mol/L and 15 to 30  $\mu$  mol/L, respectively.<sup>5</sup> Atherosclerosis is usually evaluated by structural or functional changes in the main arteries; the carotid intima-media thickness (IMT) is the best marker to detect early atherosclerotic vascular lesions.<sup>6</sup> Abnormalities of color Doppler sonography as indices of intrarenal arteries, such as the resistive index (RI) and the pulsatility index, may result from atherosclerosis in the intraparenchymal arteries.<sup>7</sup> Among 33 patients who underwent renal biopsy, RI correlated with histologically proven arteriosclerosis in the intrarenal vessels.<sup>8</sup> In addition, elevated serum or plasma Hcy concentrations have been

reported to be independent risk factors for cardiovascular disease events and atherosclerosis. [9], [10] and [11] To clarify these relationships, we performed a cross-sectional study of renal transplant recipients to determine whether serum Hcy concentrations correlated with clinical and paraclinical parameters, or with structural or functional changes in the carotid and renal arteries.

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## Materials and Methods

### Patients

The study population consisted of 47 unrelated living renal transplant recipients (30 males, 17 females) who were studied at least 6 months after transplantation with serum creatinine concentrations  $<2$  mg/dL. None of these patients received folic acid, vitamin B<sub>12</sub>, or vitamin B<sub>6</sub> supplementation. None had a history of smoking. All patients were taking cyclosporine and prednisolone plus mycophenolate mofetil (MMF) ( $n = 37$ ) or azathioprine ( $n = 10$ ).

### Laboratory Measurements

Serum concentrations of creatinine, low-density lipoprotein, high-density lipoprotein, triglycerides, uric acid, and C-reactive protein, as well as blood hemoglobin concentrations, were measured using standard methods. Blood samples were drawn after a 12-hour fast.

Cyclosporine trough levels were measured by automated clinical chemistry. Serum Hcy concentrations were measured by enzyme-linked immunosorbent assay (IBL Company, Hamburg, Germany). Hyperhomocysteinemia was defined as a serum Hcy  $\geq 15$   $\mu$ mol/L.

### Doppler Examination

The carotid arteries and intrarenal RI were examined with a 7-MHz linear probe and a 3.5-MHz convex-array transducer, respectively, using an Aloka SSD-1700 machine. All Doppler examinations were performed by a single investigator, who was blinded to the patient's history and laboratory findings. For carotid arteries, the B-mode scanning protocol included the right and left common carotid arteries (3-cm section below the carotid bifurcation) and the carotid bifurcation, as well as the internal and external carotid arteries—both 2 cm distally from the carotid bifurcation.<sup>12</sup> Maximum IMT was measured from the far wall of the common carotid artery (3-cm section before the bifurcation). Three IMT measurements of the right and left common carotid arteries were performed from the anterolateral, lateral, and posterolateral angles of the far wall. Consequently, the IMT ascribed to each subject represented the mean of six measurements. IMT was not measured at the carotid bulb or at the site of a carotid plaque. Intrarenal Doppler spectra were obtained from the interlobar and segmental arteries at three representative locations. RI was calculated using the formula:  $RI = (\text{peak systolic frequency shift} - \text{minimum diastolic frequency shift}) / \text{peak systolic frequency shift}$ . An average RI was computed to yield an overall RI for each renal transplant patient.

### Statistical Analysis

Student *t* test was used to compare independent samples and continuous variables with normal distribution. Chi-square or Fisher exact tests were used for categorical variables. Pearson coefficient was used for correlation analysis. Multiple linear regression analysis was used to assess the independent effects of age, sex, transplant duration, body mass index (BMI), mean arterial pressure (MAP), graft function, and cyclosporine trough level on serum Hcy levels. Statistical significance was established at  $P < .05$ . All data were analyzed with SPSS13.

### Results

The mean serum Hcy concentration in 47 study subjects was  $21.7 \pm 8.4 \mu\text{mol/L}$  (range =  $5.8 - 48 \mu\text{mol/L}$ ), with 37 (79%) having hyperhomocysteinemia. [Table 1.](#) shows the correlation between serum Hcy level and various parameters. Serum Hcy was significantly higher among males than females ( $23.5 \pm 9$  vs  $17 \pm 6.3 \mu\text{mol/L}$ ;  $P = .034$ ).

Table 1. Correlation Between Serum Homocysteine Concentration and the Demographic and Clinical Characteristics of Renal Transplant Recipients

Parameter	<i>r</i>	<i>P</i>
Age (y)	.06	.7
BMI	.43	.002
Transplant duration (mo)	-.05	.7
MAP (mm Hg)	-.18	.23
Serum creatinine (mg/dL)	.32	.028
Cyclosporine trough level (ng/mL)	.44	.005

BMI, body mass index; MAP, mean arterial pressure.

Multivariate logistic regression analysis showed that only BMI ( $P = .003$ ) and cyclosporine trough level ( $P = .0037$ ) were significant independent predictors of serum Hcy concentrations. There were no significant correlations between serum Hcy and age ( $P = .9$ ), sex ( $P = .18$ ), duration of transplant ( $P = .86$ ), MAP ( $P = .94$ ), or serum creatinine concentration ( $P = .2$ ). The relationship between serum Hcy concentration, several atherosclerotic risk factors, intrarenal RI, and carotid IMT are shown in [Table 2.](#)

Table 2. Clinical and Paraclinical Characteristics and Doppler Results of Transplant Recipients, Relative to Serum Homocysteine Concentration ( $n = 47$ )

Parameter	Homocysteine $\geq 15 \mu\text{mol/L}$ ( $n = 37$ )	Homocysteine $< 15 \mu\text{mol/L}$ ( $n = 10$ )	<i>P</i> Value
Gender (M/F), <i>n</i>	25/12	5/5	.46
Diabetes mellitus, <i>n</i> (%)	7 (18%)	6 (50%)	.5
MAP (mm Hg)	$88 \pm 14.3$	$94 \pm 16.9$	.34
Cellcept/azathioprine ( <i>n</i> )	32/5	5/5	.017
Hemoglobin (g/dL)	$13.7 \pm 2.4$	$13.6 \pm 1.41$	.86
LDL (mg/dL)	$100 \pm 40.9$	$109 \pm 60.2$	.57
HDL (mg/dL)	$52 \pm 20.1$	$54 \pm 12.8$	.76

Parameter	Homocysteine $\geq$ 15 $\mu\text{mol/L}$ ( $n = 37$ )	Homocysteine $<$ 15 $\mu\text{mol/L}$ ( $n = 10$ )	<i>P</i> Value
TG (mg/dL)	176 $\pm$ 74.3	179 $\pm$ 104.9	.9
CRP $\geq$ 5 (mg/L), <i>n</i> (%)	4 (11%)	3 (27%)	.3
Uric acid (mg/dL)	6.4 $\pm$ 1.38	5.6 $\pm$ 1.79	.14
Carotid IMT (mm)	0.78 $\pm$ 0.348	0.77 $\pm$ 0.419	.95
Intrarenal RI	0.7 $\pm$ 0.06	0.7 $\pm$ 0.06	.85

MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; CRP, C-reactive protein; IMT, intima media thickness; RI, resistive index.

## Discussion

Our finding of a high prevalence of hyperhomocysteinemia among transplant recipients agrees with previous studies. [1] and [4] For example, although serum Hcy decreased after transplantation, this reduction was far smaller than that expected following restoration of renal function; therefore, other factors increase serum Hcy.<sup>13</sup>

To explore the effects of different variables on serum Hcy levels, we performed a multivariate analysis. Using this model, we observed that the only factors independently influencing Hcy were cyclosporine trough level and BMI. Although several studies have shown positive correlations between Hcy and cyclosporine levels, [13], [14] and [15] others have not. [16] and [17]

The frequency of hyperhomocysteinemia was greater among patients taking MMF than those on azathioprine. Although there have been no previous comparisons of hyperhomocysteinemia in patients taking azathioprine with those taking MMF, azathioprine has been reported to have no effect on Hcy metabolism. [4] and [18] In contrast, MMF has been reported to play a positive role on Hcy metabolism by decreasing Hcy export by human proximal tubule epithelial cells in vitro.<sup>19</sup>

To our knowledge, a positive correlation between BMI and Hcy level has not been reported previously. Additional studies are therefore needed to confirm this observation.

Upon multivariate analysis, there was no correlation between serum creatinine level and Hcy concentrations. In contrast, several other studies have shown such a correlation. [20], [21] and [22] The difference may be due to subject selection. We enrolled only patients with serum creatinine <2 mg/dL.

We explored whether serum Hcy concentrations correlated with simultaneous intrarenal RI and carotid IMT measurements, which are markers for atherosclerotic vascular lesions. [6] and [23] In addition, elevated serum Hcy has been reported to be an independent risk factor for cardiovascular events and atherosclerosis.<sup>10</sup> We therefore expected that transplant recipients with hyperhomocysteinemia would show higher RI and carotid IMT than those without hyperhomocysteinemia. However, consistent with previous studies, [24] and [25] we did not observe this correlation. Prospective cohort studies are needed to determine the influence of serum Hcy on carotid IMT and intrarenal RI. We also observed that patients with and without hyperhomocysteinemia showed no differences in atherosclerotic risk factors, such as male sex, diabetes, and lipid profiles.

This study had several limitations. For example, we did not measure serum folate concentrations in renal transplant recipients. Serum folate has been reported to influence serum Hcy concentrations, although other studies have not shown such a correlation.<sup>14</sup> Moreover, none of our patients received folic acid supplementation.

In summary, we have shown herein that serum Hcy levels in renal transplant recipients correlate with higher cyclosporine trough levels and with obesity. Hyperhomocysteinemia was more common among patients taking MMF than in those taking azathioprine. However, hyperhomocysteinemia had no effect on intrarenal RI or carotid IMT.


## References

1.


- [1](#)

- A.G. Bostom, R.Y. Gohh, P. Morrissey
- **Hyperhomocysteinemia in chronic renal transplant recipients**
- Graft, 3 (2000), p. 195


2.

- 
- [2](#)
- J.V. Woodside, D.G. Fogarty, J.H. Lightbody *et al.*
- **Homocysteine and B-group vitamins in renal transplant patients**
- Clin Chim Acta, 282 (1999), p. 157


3.

- 
- [3](#)
- D. Ducloux, V. Fournier, J.M. Rebibou *et al.*
- **Hyperhomocyst(e)inemia in renal transplant recipients with and without cyclosporine**
- Clin Nephrol, 49 (1998), p. 232

4.

- 
- [4](#)
- A.G. Bostom, R.Y. Gohh, M.Y. Tsai *et al.*
- **Excess prevalence of fasting and postmethionine-loading hyperhomocysteinemia in stable renal transplant recipients**
- Arterioscler Thromb Vasc Biol, 17 (1997), p. 1894


5.

- 
- [5](#)
- S.S. Kang, P.W. Wong, M.R. Malinow
- **Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease**




- Annu Rev Nutr, 12 (1992), p. 279


6.

- 
- 6
- P.C. Simons, A. Algra, M.L. Bots *et al.*
- **Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients**The SMART Study (Second Manifestations of ARTERial disease)
- Circulation, 31 (1999), p. 951


7.

- 
- 7
- R. Pontremoli, F. Viazzi, C. Martinoli *et al.*
- **Increased renal resistive index in patients with essential hypertension: a marker of target organ damage**
- Nephrol Dial Transplant, 14 (1999), p. 360

8.

- 
- 8
- R. Ikee, S. Kobayashi, N. Hemmi *et al.*
- **Correlation between the resistive index by Doppler ultrasound and kidney function and histology**
- Am J Kidney Dis, 46 (2005), p. 603

9.

- 
- 9
- D. Ducloux, C. Ruedin, R. Gibey *et al.*

- **Prevalence, determinants, and clinical significance of hyperhomocyst(e)inaemia in renal-transplant recipients**

- Nephrol Dial Transplant, 13 (1998), p. 2890



10.

- [10](#)

- D. Ducloux, G. Motte, B. Challier *et al.*

- **Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: a prospective study**

- J Am Soc Nephrol, 11 (2000), p. 134



11.

- [11](#)

- Z.A. Massy, B. Chadeaux-Vekemans, A. Chevalier *et al.*

- **Hyperhomocysteinaemia: a significant risk factor for cardiovascular disease in renal transplant recipients**

- Nephrol Dial Transplant, 9 (1994), p. 1103

- [View Record in Scopus](#)  
| [Cited By in Scopus \(118\)](#)

12.

- [12](#)

- Y. Leskinen, T. Lehtimäki, A. Loimaala *et al.*

- **Carotid atherosclerosis in chronic renal failure—the central role of increased plaque burden**


- Atherosclerosis, 171 (2003), p. 295

- [Article](#) |  [PDF \(172 K\)](#) |  
[View Record in Scopus](#)  
| [Cited By in Scopus \(23\)](#)

13.

- [13](#)
- M. Arnadottir, B. Hultberg, J. Wahlberg *et al.*
- **Serum total homocysteine concentration before and after renal transplantation**
- Kidney Int, 54 (1998), p. 1380
- [View Record in Scopus](#)  
|  
[Full Text via CrossRef](#)  
| [Cited By in Scopus \(53\)](#)

14.

- [14](#)
- A.S. Laurés, E. Gomez, V. Alvarez *et al.*
- **Influence of anticalcineurinic therapy in plasma homocysteine levels of renal transplant recipients: a prospective study**
- Transplant Proc, 35 (2003), p. 1739
- [Article](#) |  [PDF \(117 K\)](#) |  
[View Record in Scopus](#)  
| [Cited By in Scopus \(5\)](#)

15.

- [15](#)
- D.E. Cole, H.J. Ross, J. Evrovski *et al.*
- **Correlation between total homocysteine and cyclosporine concentrations in cardiac transplant recipients**
- Clin Chem, 44 (1998), p. 2307
- [View Record in Scopus](#)  
| [Cited By in Scopus \(46\)](#)

16.

- [16](#)
- M.C. Ignatescu, M. Födiger, J. Kletzmayer *et al.*
- **Is there a role of cyclosporine A on total homocysteine export from human renal proximal tubular epithelial cells?**
- *Kidney Int Suppl*, 78 (2001), p. S258
- [View Record in Scopus](#)  
| [Cited By in Scopus \(11\)](#)

17.

- [17](#)
- W.C. Winkelmayr, R. Kramar, G.C. Curhan *et al.*
- **Fasting plasma total homocysteine levels and mortality and allograft loss in kidney transplant recipients: a prospective study**
- *J Am Soc Nephrol*, 16 (2005), p. 255
- [View Record in Scopus](#)  
| [Cited By in Scopus \(28\)](#)

18.

- [18](#)
- M. Födinger, G. Wöfl, G. Fischer *et al.*
- **Effect of MTHFR 677C>T on plasma total homocysteine levels in renal graft recipients**
- *Kidney Int*, 55 (1999), p. 1072
- [View Record in Scopus](#)  
|  
[Full Text via CrossRef](#)  
| [Cited By in Scopus \(46\)](#)

19.

- [19](#)
- M.C. Ignatescu, J. Kletzmayer, M. Födinger *et al.*

- **Influence of mycophenolic acid and tacrolimus on homocysteine metabolism**

- Kidney Int, 61 (2002), p. 1894

- [View Record in Scopus](#)

- |

- [Full Text via CrossRef](#)

- | [Cited By in Scopus \(7\)](#)

20.

- [20](#)

- H. Han, J.T. Dwyer, J. Selhub *et al.*

- **Determinants of plasma total homocysteine levels in Korean chronic renal transplant recipients**

- J Ren Nutr, 10 (2000), p. 202

- 

21.

- [21](#)

- D. Ducloux, G. Motte, N.U. Nguyen *et al.*

- **Homocysteine, nutritional status and insulin in renal transplant recipients**

- Nephrol Dial Transplant, 17 (2002), p. 1674

- [View Record in Scopus](#)

- |

- [Full Text via CrossRef](#)

- | [Cited By in Scopus \(6\)](#)

22.

- [22](#)

- T.B. Drüeke, Z. Abdulmassih, B. Lacour *et al.*

- **Atherosclerosis and lipid disorders after renal transplantation**

- Kidney Int Suppl, 31 (1991), p. S24

○

23.

○ [23](#)

○ Y. Shimizu, T. Itoh, H. Hougaku *et al.*

○ **Clinical usefulness of duplex ultrasonography for the assessment of renal arteriosclerosis in essential hypertensive patients**

○ Hypertens Res, 24 (2001), p. 13

○ [View Record in Scopus](#)

|

[Full Text via CrossRef](#)

| [Cited By in Scopus \(23\)](#)

24.

○ [24](#)

○ B. Suwelack, U. Gerhardt, J. Witta *et al.*

○ **Effect of homocysteine on carotid intima-media thickness after renal transplantation**

○ Clin Transplant, 14 (2000), p. 555

○ [View Record in Scopus](#)

| [Cited By in Scopus \(8\)](#)

25.

○ [25](#)

○ S. Brzósko, U. Lebkowska, J. Malyszko *et al.*

○ **Correlation between carotid intima-media thickness and hematocrit and hemoglobin values in renal transplant recipients**

○ Clin Transplant, 15 (2001), p. 349